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IN-VITRO PRIMING OF HUMAN LYMPHOCYTES TO HETEROLOGOUS INSULINS
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RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have developed an in vitro priming assay in which peripheral blood lymphocytes from normal subjects are primed with insulin for 14 days prior to challenge with insulin in conjunction with autologous antigen-presenting cells for a further 5 days. Sheep, beef and pork insulins possess, respectively, four, three and one amino acid differences from the human molecule (out of a total of 51 residues) and the magnitude of the response to priming correlates with the degree of sequence variation. Although human insulin produces little response, priming with heterologous insulins readily induces auto-immunization on secondary challenge. The response to porcine priming was enhanced if the secondary cultures were challenged with bovine or ovine insulin i.e., a heteroclitic response was observed. Individual donors differ in their response to priming and high responders possess the HLA-DR7 glycoprotein more frequently than low responders. This is in keeping with previous studies on antibody production in vivo and probably relates to the ease with which individual class II glycoproteins complex with processed antigen and stimulate T cells. This method has considerable potential for screening novel insulin molecules and formulations and should facilitate the mapping of helper and **suppressor epitopes** as well as the identification and agretopes involved in the presentation of insulin to T cells.

DESCRIPTORS: ANTIDIABETIC-DRUG IMMUNOGENICITY AUTOIMMUNIZATION HETEROCLITIC RESPONSE
CONCEPT CODES:
13020 Metabolism-Metabolic Disorders
15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
17008 Endocrine System-Pancreas
22005 Pharmacology-Clinical Pharmacology (1972-)
22016 Pharmacology-Endocrine System
22504 Toxicology-Pharmacological Toxicology (1972-)
34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
02508 Cytology and Cytochemistry-Human
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
32600 In Vitro Studies, Cellular and Subcellular
BIOSYSTEMATIC CODES:
86215 Hominidae
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA):
Animals
Chordates
Vertebrates
Mammals
Primates
Humans

09081526 BIOSIS NO.: 199497089896
Epitopes of myelin basic protein that trigger TGF-beta release after oral tolerization are distinct from encephalitogenic epitopes and mediate epitope-driven bystander suppression.
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JOURNAL: Journal of Immunology 151 (12):p7307-7315 1993
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have been studying the suppression of experimental autoimmune encephalomyelitis in the Lewis rat after oral administration of myelin basic protein (MBP). Suppression is mediated by CD8+ T cells that adoptively transfer protection and suppress immune responses in vitro. This suppression is mediated by secretion of TGF-beta following triggering by the fed antigen. In the present study, we tested the ability of overlapping 20 amino acid peptides from MBP to trigger suppression mediated by spleen cells from Lewis rats orally tolerized to MBP. Using a transwell system, we found that spleen cells from MBP orally tolerized animals stimulated by residues 21-40, 51-70 and 101-120 of MBP suppress proliferative responses of an ovalbumin specific cell line. This suppression correlated with secretion of TGF-beta by cells stimulated with the peptide. In addition, T cells from animals fed the tolerogenic peptide 21-40 alone secreted TGF-beta whereas no TGF-beta release or in vitro suppression was observed in animals fed the MBP encephalitogenic determinant 71-90. The 71-90 peptide triggered proliferation of MBP primed cells from animals immunized with MBP/CFA whereas the **suppressor epitopes** identified above did not. Furthermore, oral administration of peptide 21-40 suppressed disease induced by peptide 71-90. DTH responses to 71-90 were not affected by oral administration of peptide 21-40 whereas DTH responses to whole MBP were suppressed. These results demonstrate that distinct suppressor determinants exist on MBP which are separate from encephalitogenic determinants, and that epitope-driven bystander suppression plays an important role in down-regulation of tissue specific autoimmune processes following oral tolerization. These findings have important implications for the design of tissue specific targeted immunotherapy by oral tolerization in humans.
DESCRIPTORS:
MAJOR CONCEPTS: Blood and Lymphatics (Transport and Circulation); Endocrine System (Chemical Coordination and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Nervous System (Neural Coordination); Pathology
BIOSYSTEMATIC NAMES: Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: rat (Muridae)
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
MISCELLANEOUS TERMS: AUTOIMMUNE ENCEPHALOMYELITIS; CD8 T-CELLS; IMMUNOTHERAPY; TRANSFORMING GROWTH FACTOR
CONCEPT CODES:
12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
12512 Pathology, General and Miscellaneous-Therapy (1971-)
15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies

9512334 BIOSIS Number: 94017334

EXPRESSION OF HETEROLOGOUS PEPTIDES AT TWO PERMISSIVE SITES OF THE MALE PROTEIN ANTIGENICITY AND IMMUNOGENICITY OF FOREIGN B-CELL AND T-CELL EPITOPES

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GENE (AMST) 113 (1). 1992. 35-46. CODEN: GENED
Full Journal Title: GENE (Amsterdam)
Language: ENGLISH

We previously determined a number of 'permissive' sites in the periplasmic maltose-binding protein (MalE) from Escherichia coli. These sites accept the insertion of heterologous peptides without major deleterious consequences for the activities, structure and cellular location of the protein. This study explores the versatility of two such permissive sites for the synthesis of foreign peptides, and examines the antigenicity and the immunogenicity of the inserts. One site is located after amino acid 133 (aa133) of MalE, and the other after aa303. Both sites tolerate inserts of up to at least 70 aa and accept sequences of different natures. Hydrophobic aa sequences are accepted, although strongly hydrophobic sequences, such as the Sendai virus F protein membrane anchor, affected export. We compared the antigenic and the immunogenic properties of peptides derived from the coat proteins of HBV and poliovirus which contain well defined B-cell epitopes. Specific monoclonal antibodies show that the antigenic properties of the inserted B-cell epitopes were different at the two sites. Despite these differences, the inserted peptides elicited strong and comparable antibody responses in mice against the corresponding synthetic peptides. In this case, and with these criteria, the molecular context of the peptides did not affect the immunogenicity of B-cell epitopes. We show for the first time that when a foreign peptide carrying a T-cell epitope was inserted in MalE, the hybrid proteins can elicit a T-cell response against the foreign peptide both in vivo and in vitro. Furthermore, the MalE hybrid was a efficient as free peptide in simulating T-cell hybridomas in vitro. The MalE vectors provide a powerful genetic system to study how the position and the conformation of a peptide within a protein affect the B-cell and T-cell responses.

Descriptors/Keywords: MOUSE ESCHERICHIA-COLI HEPATITIS B VIRUS POLIOVIRUS SENDAI VIRUS F PROTEIN AMINO ACID SEQUENCE MOLECULAR SEQUENCE DATA ANTIBODY RESPONSE
Concept Codes:

bacterial proteins expressing
several copies of a viral T cell epitope

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European Journal of Immunology 23 (11). 1993. 2998-3002.
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Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 002 Ref. 017757

A viral T cell epitope was genetically inserted within the periplasmic MalE protein of Escherichia coli in two different permissive insertion sites and resulting hybrid proteins were used to study the in vitro and in vivo immunogenicity of the foreign T cell epitope. Purified hybrid MalE proteins containing the T cell epitope 120-132 (PreS:T) from PreS2 region of hepatitis B virus HBsAg inserted alone or with its adjacent B cell epitope (132-145) were able to induce strong peptide-specific T cell responses in mice. In vitro stimulation of primed lymph node cells or specific T cell hybridomas by the hybrid proteins required processing of the inserted T cell epitope and was inhibited by antigen-presenting cells fixation. The inserted T cell epitope was presented in vitro, in association with appropriate major histocompatibility complex molecules, as efficiently as free synthetic peptide. The in vitro immunogenicity of MalE hybrid proteins was increased by inserting four tandemly repeated copies of PreS:T, either at site 133 or 303. These results were confirmed in vivo by comparing the proliferative responses of lymph node cells from DBA/1 mice primed with MalE hybrid proteins containing one or four copies of PreS:T. Thus, the use of MalE hybrid proteins expressing multiple copies of a given foreign T cell epitope allows the induction of peptide-specific T cell response with a lower dose of priming antigen.

Descriptors/Keywords: RESEARCH ARTICLE; ESCHERICHIA COLI; MURINE; PERMISSIVE INSERTION SITE; HYBRID MALE PROTEIN; IMMUNOGENICITY; HEPATITIS B VIRUS SURFACE ANTIGEN PRES2 REGION; B CELL; LYMPH NODE CELL PROLIFERATIVE RESPONSE; PEPTIDE-SPECIFIC T LYMPHOCYTE REACTIVITY; PRIMING ANTIGEN; RECOMBINANT VACCINE RELEVANCE; GENETIC ENGINEERING

Concept Codes:
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*31000 Physiology and Biochemistry of Bacteria
*31500 Genetics of Bacteria and Viruses
*33506 Virology-Animal Host Viruses
*34504 Immunology and Immunochemistry-Bacterial, Viral and Fungal
*34508 Immunology and Immunochemist

OSIS Number: 95071013

PRESENTATION OF A VIRAL T CELL EPITOPE EXPRESSED IN THE CDR3 REGION OF A SELF IMMUNOGLOBULIN MOLECULE

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SCIENCE (WASHINGTON D C) 259 (5092). 1993. 224-227. CODEN: SCIEA
Full Journal Title: SCIENCE (Washington D C)
Language: ENGLISH

Synthetic peptides corresponding to microbial epitopes stimulate T cell immunity but their immunogenicity is poor and their half-lives are short. A viral epitope inserted into the complementarity-determining region 3 (CDR3) loop of the heavy chain of a self immunoglobulin (Ig) molecule was generated from the Ig context and was presented by I-Ed class II molecules to virus-specific, CD4+ T cells. Chimeric Ig-peptide was presented 100 to 1000 times more efficiently than free synthetic peptide and was able to prime virus-specific T cells in vivo. These features suggest that antigenized Ig can provide an improved and safe vaccine for the presentation of microbial and other peptides.

Descriptors/Keywords: COMPLEMENTARY-DETERMINING REGION 3 T-CELL AUTOIMMUNITY VACCINATION

6 BIOSIS Number: 97328446

Molecular context of a viral T cell determinant within a chimeric bacterial protein alters the diversity of its T cell recognition

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Print Number: Biological Abstracts Vol. 098 Iss. 003 Ref. 034958

We genetically introduced two different viral CD4+ T cell epitopes within two internal sites of the Escherichia coli maltose-binding (Ma)E) protein. Affinity-purified hybrid MalE proteins were used to analyze the influence of the molecular environment on the presentation of inserted epitope to T cells. In the first model, the 120 to 132 PreS T cell epitope was inserted alone or with its C-terminal B cell epitope (132-145) at site 133 or 303 of MalE. The maltose-binding protein with PreS peptide inserts expressing the 120 to 132 sequence were able to induce in vivo and in vitro peptide-specific T cell response, whatever the length and the position of the insert. In the second model, the 103 to 115 T cell epitope from the C3 region of poliovirus type 1 (PV1) was inserted, with various flanking sequences, either at site 133 or 303 of MalE protein. The longer C3:86 to 115 insert induced poliovirus-specific T cell responses at both sites of MalE, whereas the C3:93 to 115 insert did it only at site 303 but riot at site 133. Moreover, C3:103 to 115 specific T cell hybridomas discriminated between the processed peptides generated from the different chimeric proteins, as a result of differences in the length and the position of the inserted sequence. Therefore, in this experimental model the loss of in vivo immunogenicity of an antigenic determinant within a chimeric protein is related to the activation of a reduced T cell repertoire. These observations involve important consequences for the engineering of recombinant vaccines.

Descriptors/Keywords: RESEARCH ARTICLE; ESCHERICHIA COLI; MALE PROTEIN INSERTION; HEPATITIS B VIRUS PRES T CELL EPITOPE; B CELL EPITOPE; POLIOVIRUS C3 REGION T CELL EPITOPE; INSERT LENGTH DEPENDENT; INSERT POSITION DEPENDENT; RECOMBINANT VACCINE RELEVANCE; GENETIC ENGINEERING
Concept Codes:
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
*15004 Blood, Bl

10875238 BIOSIS Number: 97075238

Immunodominance of a recombinant T-cell epitope depends on its molecular environment

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Molecular Immunology 30 (17). 1993. 1561-1572.

Full Journal Title: Molecular Immunology

ISSN: 0161-5890

Language: ENGLISH

Print Number: Biological Abstracts Vol. 097 Iss. 004 Ref. 042748

In the present study, we have investigated the influence of the molecular environment of a T-cell epitope on its immunogenicity. We genetically inserted into different sites of two bacterial recipient proteins, LamB or MalE, an immunodominant T-cell epitope: the 120-132 T-cell epitope from the PreS2 region of HBV. The T-cell epitope was introduced, either alone (PreS:T) or with an adjacent B-cell epitope (PreS:TB). After purification, the hybrid proteins were injected into mice and we studied the immunogenicity of recombinant T-cell epitopes by analyzing the in vitro proliferative responses of LN cells from these mice to the inserted peptides. The immunization of mice with recombinant MalE protein containing the PreS:T or PreS:TB peptides at two different sites induced strong peptide-specific proliferative responses, indicating that the insertion sites did not affect the immunodominance of the inserted T-cell epitope. A strong T-cell proliferative response was also obtained after immunization of mice with hybrid LamB protein containing the PreS:TB epitope at position 153. In contrast, the recombinant proteins which contained only the PreS:T epitope at positions 153 or 374 failed to stimulate T-cell responses. Therefore, this study demonstrates that the immunogenicity of recombinant T-cell epitopes may be strongly affected both by the insertion site and by inserted adjacent residues.

Descriptors/Keywords: RESEARCH ARTICLE; MOUSE; IMMUNOGENICITY; INSERTION SITE; INSERTED ADJACENT RESIDUES

Concept Codes:

*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10068 Biochemical Studies-Carbohydrates
*10506 Biophysics-Molecular Properties and Macromolecules
*10508 Biophysics-Membrane Phenomena
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*34502 Immunology and Immunochemistry-General; Methods
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
10054 Biochemical Methods-Proteins, Peptides and Amino Acids
10058 Biochemical Methods-Carbohydrates

Biosystematic Codes:

86375 Muridae

Super Taxa:

Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

?

5,114,713, May 19, 1992, P. falciparum CS-peptides as universal **T**-**cell** **epitope**; Francesco Sinigaglia, 424/191.1, 268.1, 272.1; 530/324, 326, 350, 806 [IMAGE AVAILABLE]

US PAT NO: 5,114,713 [IMAGE AVAILABLE] L3: 28 of 33

ABSTRACT:
The present invention relates to the use of a peptide from the circumsporozoite (CS) protein of Plasmodium falciparum (P. falciparum) and the derivatives thereof as a universally recognized **T**-**cell** **epitope** i.e. an epitope which is recognized in association with many different human and mouse major histocompatibility complex (MHC) haplotypes e.g. in the context of the human MHC class II molecules such as DR1, DR2, DR4, DR5, DRw6, DR7 or DR9. Furthermore the present invention relates to the above-mentioned peptide per se and to immunogenic compositions comprising such a peptide or a derivative thereof. These immunogenic compositions can be used as vaccines to elicit a durable immune response against a pathogenic agent in humans and animals irrespective of the MHC haplotype of the host.

. 5,500,366, Mar. 19, 1996, Polynucleotide encoding **T**-**cell** **epitopes** of the protein TraT; Gregory J. Russell-Jones, et al., 435/252.3; 424/190.1, 192.1; 435/69.3, 240.2, 254.11, 320.1; 536/23.4, 23.7 [IMAGE AVAILABLE]

US PAT NO: 5,500,366 [IMAGE AVAILABLE] L3: 6 of 33

ABSTRACT:

T-**cell** **epitopes** of or derived from the TraT protein of E. coli have been identified and used in the preparation of complexes with immunogens to enhance or provide immune responses to the immunogens. The complexes can be prepared directly, by chemical linkage, or as fusion proteins. In the latter context, polynucleotides encode a fusion protein which a transformed host can express. The fusion proteins may be expressed intracellularly or exported to and expressed on the surface of the transformant host.